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Two different signaling mechanisms involved in the excitation of rat sympathetic neurons by uridine nucleotides.

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UTP stimulates transmitter release and inhibits M-type K(+) channels in rat superior cervical ganglion neurons via G protein-coupled P2Y receptors. To investigate the underlying signaling mechanisms, we treated the neurons with either pertussis or cholera toxin; neither treatment altered the inhibition of M-type K(+) channels by 10 microM UTP. However, pertussis toxin reduced UTP-evoked [(3)H]noradrenaline release by 66%. UTP, UDP, ATP, and ADP caused accumulation of inositol trisphosphate in a pertussis toxin-insensitive manner. Pharmacological inhibition of inositol trisphosphate-induced Ca(2+) release (by inhibition of phospholipase C, of inositol trisphosphate receptors, and of the endoplasmic Ca(2+)-ATPase) prevented the UTP-dependent inhibition of M currents but failed to alter UTP-evoked [(3)H]noradrenaline release. Chelation of intracellular Ca(2+) by 1,2-bis(2-aminophenoxy)ethane-N, N,N',N'-tetraacetic acid also reduced the inhibition of M currents by UTP. In addition, all these manipulations attenuated the inhibition of M currents by bradykinin, but hardly affected the inhibitory action of oxotremorine M. These results demonstrate that UTP inhibits M-type K(+) channels via an inositol trisphosphate-dependent signaling cascade that is also used by bradykinin but not by muscarinic acetylcholine receptors. In contrast, the secretagogue action of UTP is largely independent of this signaling cascade but involves pertussis toxin-sensitive G proteins. Thus, UTP-sensitive P2Y receptors excite sympathetic neurons via at least two different signal transduction mechanisms.

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